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A possible role of receptors in the SLIT/ROBO and NETRIN/DCC pathways in the genesis of multiple sclerosis

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Abstract The medial longitudinal fascicle and the optic nerve are often affected in multiple sclerosis which causes internuclear ophthalmoplegia and optic neuritis. During prenatal development axons of both neuronal pathways are subjected to midline crossing in the central nervous system. Transmembrane receptor proteins like robos and dcc that interact with the chemorepellents and attractants slit and netrin are expressed in developing axons that cross the midline and are likely to play a role postnatally. It is hypothesized and discussed that these receptor proteins represent a specific antigen targeted by autoimmune processes in multiple sclerosis.

Introduction

Internuclear ophthalmoplegia and optic neuritis are common signs of multiple sclerosis.

Internuclear ophthalmoplegia is an eye motility disorder caused by defects in internuclear neurons that run in the brainstem between the nuclei of the sixth and third cranial nerves. The cell bodies of these neurons lie close to the motoneurons of the abducent nerve that supplies the ipsilateral abducting eye muscle, i.e. the lateral rectus muscle. At the level of the abducent nucleus the axons of the internuclear neurons cross the midline and ascend to a contralateral motoneuron subgroup of the oculomotor nerve nucleus that supplies the medial rectus eye muscle on its side. These abducens internuclear neurons are required for lateral gaze: along with the abducent motoneurons they receive input from horizontal gaze centers and mediate the conjugate movements of the contralateral medial rectus. Thus the contralateral medial rectus contracts together with the ipsilateral lateral rectus to shift both eyes to the same direction. If these internuclear neurons that ascend within the medial

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longitudinal fascicle and that in man span a distance of about 2.5 cm are disturbed, internuclear ophthalmoplegia occurs, that means on intended side gaze the eye on the side to which gaze is directed is abducted by the intact abducent nerve but the fellow eye is not adducted. Consequently the eyes deviate on lateral gaze and diplopia results. Contraction of the medial rectus during convergence of the eyes is unaffected in internuclear ophthalmoplegia for the motoneuron subgroup supplying the medial rectus itself is intact and the impulse for convergence stems from gaze centers not involving the medial longitudinal fascicle. Also vertical gaze is unaffected in internuclear ophthalmoplegia.

Internuclear ophthalmoplegia occurs in nearly 30% of patients with multiple sclerosis at some time during the disease [1], not rarely as a first symptom. Optic neuritis is reported to occur in 50% of patients at some time during the disease, in about 15—20% of patients with multiple sclerosis it is the initial symptom of the disease [2]. Thus both affections of the longitudinal fascicle and of the optic nerve may occur in early stages of the disease. Working in neuroophthalmology one feels challenged to investigate whether these two structures share common features that make them prone to a possibly common pathogenetic mechanism.

Recent findings in a congenital oculomotor disease that at first glance has nothing in common with multiple sclerosis might hold a clue to this question.

In 2004 Jen and coworkers reported that mutations in the gene *ROBO3* that encodes a transmembrane receptor molecule that normally seems to promote midline crossing of some hindbrain axons account for the clinical picture of familial Horizontal Gaze Palsy with Progressive Scoliosis, HGPPS [3]. In this congenital disease horizontal gaze to both sides is disturbed whereas convergence and vertical eye movements are mainly unaffected. Abnormal or absent crossing in motor and somatosensory paths has been found in these patients. The progressive scoliosis in these patients is discussed to be of primary neurodevelopmental origin by misinnervation of the paraspinal muscles due to inhibited crossing of the supplying nerve fibres but also other mechanisms are possible. NMR studies revealed pontine and medullar abnormalities. A diffusion tensor imaging study revealed noncrossing of major fiber tracts in the pons and no decussation of superior cerebellar peduncles in a patient with Horizontal Gaze Palsy with Progressive Scoliosis and a mutation in the *ROBO3* gene. The corpus callosum as a main structure of crossing fibres for interhemispheric connections was found unaffected. See references [3—5].

Robo3 encodes a transmembrane receptor interacting in the slit/robo signalling pathway that is important in the process of axonal pathfinding in the development of central nervous structures. *Slits* and *netrin* encode molecules expressed in the midline of the nervous system and some growing neurons express receptors that interact with them. Generally, maybe with exceptions, proteins of the slit group act as repellents from the midline and netrin acts as an attractant. In the developing brain an intricate interplay between slits and the receptors of the robo-group and dcc (deleted in colorectal cancer) that is a netrin receptor guides growing axons either away from or across the midline [6—9].

The lesions occurring with a mutation in *ROBO3* thus seem confined to crossing structures in the brainstem including the pyramidal tract and somatosensory tracts. From a neuroophthalmologic point of view the clinical picture of a blockade of horizontal gaze with intact convergence in the absence of normal pontine crossings could be contributed to a defective crossing of the abducens internuclear neurons that run normally to the contralateral oculomotor subnucleus. As the clinical studies on the other neurological deficiencies in this disease show it seems to be possible that fibres that do not cross properly find ipsilateral targets. Thus abducens internuclear neurons that because of the genetic defect do not cross would run to the ipsilateral third nerve oculomotor subgroup supplying the medial rectus and a coinnervation of the ipsilateral lateral and medial rectus of one eye would result leading to blockage of horizontal eye movements. Horizontal gaze palsy with progressive scoliosis is encompassed under the entity of so called congenital cranial dysinnervation disorders in which misinnervations occur by neurodevelopmental defects [10]. Although the clinical picture of horizontal eye movements in congenital HGPPS at first view does not resemble the picture of an acquired bilateral lesion of the abducens internuclear neurons as it occurs in bilateral internuclear ophthalmoplegia where adduction on horizontal sidegaze is limited but abduction is free, the motility pattern in HGPPS might as well be caused by a primary disturbance of the abducens internuclear neurons which is overlayed by secondary misinnervation phenomena.

So in this congenital disease caused by a mutation in the *ROBO3* gene a defect occurs on neuronal structures crossing the midline in the lower brainstem, namely the pyramidal tract, somatosensory tracts and presumably abducens internuclear neurons. Supposably these structures express the transmembrane receptor ROBO3.

Thus one could postulate that a special feature of abducens internuclear neurons and their axons running in the medial longitudinal fascicle is that they express or developmentally expressed transmembrane proteins that interact in the ROBO/SLIT signalling pathway.

The Hypothesis

I hypothesize that in multiple sclerosis transmembrane proteins involved in the ROBO/SLIT signalling pathway are targeted by an autoimmune process.

Not necessarily ROBO3 has to be this target.

A closer look to the signalling pathways involving the slits, the receptors of the robo-group and netrin [9] shows that robo3 closely interacts with two other transmembrane receptors, robo1 and dcc that are also expressed by axons expressing robo3. As large transmembrane proteins all three have features that likely could make them prone to an autoimmune reaction.

Discussion

According to the hypothesis internuclear ophthalmoplegia in multiple sclerosis would result from an autoimmune reaction at the site of a transmembrane receptor on the surface of abducens internuclear neurons.